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Guidance for: The acute management of status epilepticus in adult patients

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Background

Status Epilepticus (SE) is a common medical emergency and it can occur both in patients with and without a history of epilepsy. Morbidity and mortality is high and increases with duration of uncontrolled seizures which necessitates early active treatment.[1] Despite this there is significant variation in the way SE is treated between centres and no nationally agreed guidelines for the management of SE in critical care.[2]

These guidelines are based on multi-speciality consensus agreement between acute medicine, neurology, intensive care and emergency medicine. The critical care pharmacy group provided input on pharmaco-therapeutics.

Purpose, objective and scope

Purpose

The purpose of this document is to provide guidance on the management of adult patients with SE in hospital. It provides a framework for management of SE on the acute hospital ward and Intensive Care Unit (ICU). Successful treatment of SE, especially refractory SE, requires management of the underlying cause, therefore, a significant part of this guideline is devoted to investigation and diagnosis.

Objective

This document aims to facilitate early management and provide an investigative framework to determine the underlying aetiology of seizures.

Scope

This document pertains to the management of SE in patients over the age of 16 years. It excludes the obstetric population, for whom there are other guidelines available.[3] It includes guidance on management of SE in terms of initial stabilisation, investigation, pharmacological treatment, use of sedation and transfer to critical care. We have used the International League Against Epilepsy (ILAE) definitions and classification of status epilepticus in this guideline.[4] We have also proposed a definition for levels of neurocritical care and we advise on indications for referral between these care levels.

This document is a guideline and outlines perceived best practice. It is in line with the NICE,[5] European Federation of Neurological Societies,[6] The American Epilepsy Society[7] and the Neurocritical Care Society[8] clinical guidelines for epilepsy but takes into account recently published clinical and experimental evidence regarding the pharmacological management of SE. As the evidence base in this area is evolving, we aim to update the guidance (please check The Intensive Care Society website for the most up to date version). The document is not intended to be a universally applicable protocol to all patients with SE owing to the broad range of conditions that can result in seizures. It does, however, provide a guide to the acute management of SE in the majority of patients. This guideline has been produced by clinicians in the United Kingdom and we acknowledge that there will be geographical variation in perceived best practice.

This guidance should be adopted jointly by all stakeholders involved in the acute care of patients presenting with SE. No guideline can be exhaustive or replace sound clinical judgement. Each patient should be treated as an

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individual, with early and clear communication between the multidisciplinary team members being the key to achieving the right outcome.

The working group suggest that research funders consider a best practice implementation project using a stepwedge or cluster-randomised design to evaluate uptake and efficacy of the guidelines.

Definitions

Status epilepticus (SE)

This is defined as five or more minutes of either continuous seizure activity or repetitive seizures with no intervening recovery of consciousness. SE was previously described as seizure activity or repetitive seizures lasting more than 30 min. The timeframe for the definition of SE has been revised to emphasise that prognosis worsens with increasing duration and that treatment must be started early.[9] SE is further classified as either generalised convulsive or non-convulsive in nature. Generalised convulsive SE is the more common type of SE.

Convulsive status epilepticus (CSE)

This is defined as seizures with generalised rhythmic jerking of limbs and conscious level impairment which fulfil the criteria for status epilepticus. This is an emergency and requires immediate medical attention.

Non-convulsive SE (NCSE)

The diagnosis of NCSE can be difficult due to the diversity in clinical presentation and is dependent on EEG findings. NCSE is defined as SE without a prominent (clinically obvious) motor component. NCSE with impaired consciousness has a high mortality and should be treated as CSE. NCSE can follow CSE and is an important treatable cause of coma.

In NCSE presenting as a change in mental status or behaviour from baseline, the risks are less clear and in most cases admission to critical care is not necessary. The consensus view remains that early active treatment is desirable in these patients and the majority of the recommendations in this guideline still apply.

Refractory status epilepticus (RSE)

SE that does not respond to initial pharmacological therapy (one benzodiazepine and one non-benzodiazepine anticonvulsant medication). Treatment requires admission to critical care and intravenous anaesthesia to suppress seizures.

Super-refractory status epilepticus (SRSE)

SE, which continues or recurs despite an adequate continuous infusion of intravenous (IV) anaesthetic agents for more than 24 h. Genuine super-refractory SE often occurs with underlying neurological disorders for example, autoimmune encephalitis.

New-onset refractory status epilepticus (NORSE)

A clinical presentation, rather than a specific diagnosis, in a patient without pre-existing epilepsy or relevant neurological disorder. Consists of new-onset RSE without clear structural, metabolic or toxic cause. This includes patients with viral or autoimmune causes. If no cause is found after extensive evaluation, this is defined as 'cryptogenic NORSE' or 'NORSE of unknown cause'.[10]

Febrile infection-related epilepsy syndrome (FIRES)

FIRES is a subcategory of NORSE requiring a prior febrile illness, with fever onset between 1 and 14 days prior to onset of RSE. Fever may be absent at the time of seizures.[10]

Non-epileptic attack disorder (NEAD)

NEAD (also known as dissociative seizures) is a condition where individuals experience episodes that resemble epileptic seizures but do not have a physical cause related to abnormal electrical activity in the brain. The term can lead to confusion but it is a well-recognised and common disorder that affects many patients presenting to epilepsy clinics. The dissociative seizures are often triggered by trauma or stress and the mainstay of treatment is psychological therapy.[11] These seizures can also be termed psychogenic non-epileptic seizures (PNES) or simply non-epileptic seizures (NES). The term 'pseudoseizures' is obsolete.

Definitions of neurocritical care provision

Neuro-critical care is devoted to the comprehensive care of critically ill patients with neurological or neurosurgical disease. There is no current consensus definition for levels of neurocritical care within the UK and the authors believe a UK consensus statement would be beneficial. In the interim we propose the following levels of care, taking into account existing international definitions,[12] as well as the availability of resources in the UK hospital system.

Tertiary neurocritical care service

Tertiary receiving centres for complex neurological emergencies. These are specialist neurocritical care services, able to provide definitive care for a wide variety of neurocritical care emergencies with access to advanced monitoring techniques and on-site neurosciences and neurosurgical support.

Secondary neurocritical care service

Able to stabilise acutely ill neurological emergencies and safely manage stable neurocritical care disease processes, whilst having an established advice, referral and transfer

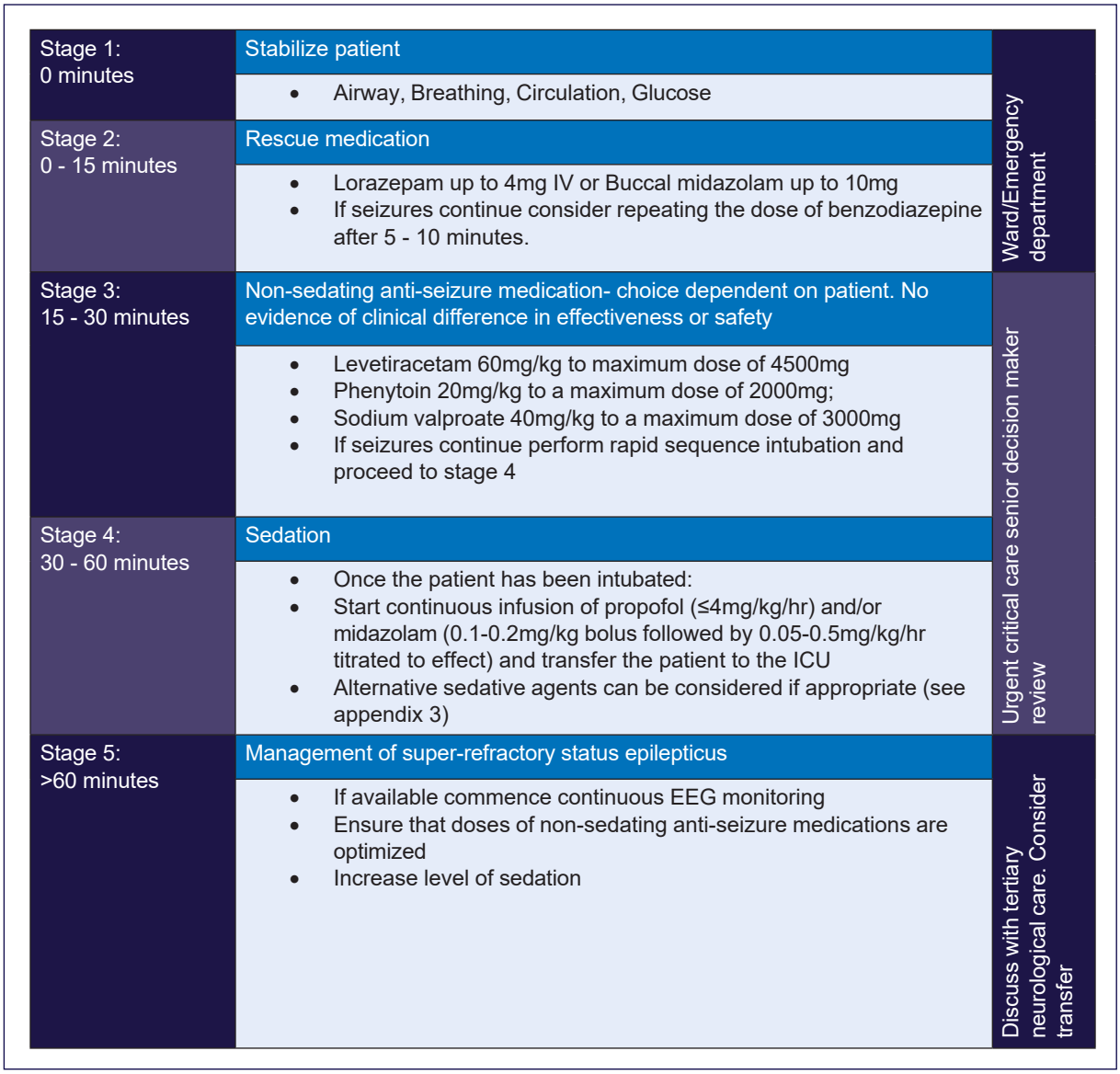
Stage 1:
0 minutes
Stabilize patient
Airway, Breathing, Circulation, Glucose
Stage 2:
0 - 15 minutes
Rescue medication
Lorazepam up to 4mg IV or Buccal midazolam up to 10mg
If seizures continue consider repeating the dose of benzodiazepine after 5 - 10 minutes.
Ward/Emergency department
Stage 3:
15 - 30 minutes
Non-sedating anti-seizure medication- choice dependent on patient. No evidence of clinical difference in effectiveness or safety
Levetiracetam 60mg/kg to maximum dose of 4500mg
Phenytoin 20mg/kg to a maximum dose of 2000mg;
Sodium valproate 40mg/kg to a maximum dose of 3000mg
If seizures continue perform rapid sequence intubation and proceed to stage 4
Stage 4:
30 - 60 minutes
Sedation
Once the patient has been intubated:
Start continuous infusion of propofol (≤4mg/kg/hr) and/or midazolam (0.1-0.2mg/kg bolus followed by 0.05-0.5mg/kg/hr titrated to effect) and transfer the patient to the ICU
Alternative sedative agents can be considered if appropriate (see appendix 3)
Urgent critical care senior decision maker review
Stage 5:
>60 minutes
Management of super-refractory status epilepticus
If available commence continuous EEG monitoring
Ensure that doses of non-sedating anti-seizure medications are optimized
Increase level of sedation
Discuss with tertiary neurological care. Consider transfer

Figure 1. At a glance guide to the management of adult patients with convulsive seizures in the acute hospital setting-applicable to all levels of neurocritical care service.[13]

pathway for patients who require Tertiary Neurocritical Care. This level encompasses the majority of critical care units in the UK.

Primary neurocritical care service

Suitable for the stabilisation and subsequent transfer of acute neurocritical care emergencies. There is limited access to specialist investigations or interventions and timely referral to a Secondary or Tertiary Neurocritical Care service should be considered if needed.

All levels of neurocritical care service should be able to initiate management of acute status epilepticus as per Figure 1.

General recommendations

1. Critical care review should be sought early if the patient fails to stop seizing following maximal dosage of benzodiazepines and an adequate dose of a non-sedating anti-seizure medication.
2. Continuous electroencephalogram (cEEG) is advised for patients with ongoing depressed consciousness or for patients in refractory status epilepticus (RSE) or super-refractory status epilepticus (SRSE). Advice should be sought from a regional neurosciences centre on management and transfer of the patient if cEEG is not available in your institution.
3. Long term anticonvulsant medication should be given in parallel with emergency treatment. Any pre-existing therapy should be continued at full dose and any recent reductions reversed.
4. If possible, please take medication levels on admission; this will help with establishing usual levels and confirming concordance. Do not omit doses whilst awaiting level to be reported. Failure to take medication as prescribed is a common cause of a patient

with epilepsy developing SE. If non-concordance with a medication is suspected then consider reloading with one of the emergency agents as per the algorithm. For information about route adjustment, and/or levels please contact your pharmacist.

5. In patients with RSE or SE of unclear cause, a neurological opinion should be sought. This should, ideally, be obtained within 24 h of admission to the critical care unit.
6. Patients with SRSE should be discussed with a tertiary neurocritical care unit and transfer should be strongly considered.
7. Those patients with SE requiring investigation or management that cannot be safely provided in a secondary neurocritical care unit should be considered for transfer to a tertiary unit.

Further management of seizures

Patients who present to hospital with SE will require admission to allow for a period of observation and to plan ongoing care. Specialist neurological opinion should be sought to advise on ongoing requirements for appropriate dosing or weaning of anti-seizure medications. A plan should be instituted for additional specialist investigations and referral to a higher level of neurocritical care service should be sought.

Critical care management process

When to consider admission to the critical care unit

Consider admission to the Critical Care Unit in the following situations:

(a) SE that requires intubation and ventilation to terminate
(b) The patient's conscious level remains sufficiently depressed after termination of seizures to impede the ability to protect their airway

When to consider admission to the critical care unit

(c) Respiratory depression that cannot be safely managed on the ward following emergency medication use (in particular with benzodiazepine therapy)
(d) The patient's physiological and metabolic derangements are significant and require monitoring or therapy that cannot adequately be provided for on a ward

Assessment process upon admission to critical care

The patient should receive a comprehensive re-assessment by a senior trainee or consultant in critical care.
Seizure frequency and duration should be meticulously documented as part of the patient's ongoing observations.

1. Airway – establish and maintain a patient airway
2. Breathing – use lung-protective ventilation for intubated patients[14]
   (a) Tidal volume 6–8 ml/kg ideal body weight, plateau pressure $< 30\ cmH_20$
   (b) PEEP $> 5\ cmH_20$ (titrated according to ARDSNet PEEP ladder)
   (c) Target $Pa0_2 > 8\ kPa$

Assessment process upon admission to critical care

3. Circulation – maintain a mean arterial pressure of 65 mmHg with optimum haemodynamic management. Pay careful attention to daily fluid balance
4. Disability – do not perform routine daily sedation holds; instead, taper sedation as described below.[15] In the absence of guidance relating to blood sugar control relevant to SE, a blood sugar value of 8–12 mmol/L is a pragmatic and likely safe choice[16]
5. Gastrointestinal – aim for early enteral nutrition and ideally within 48 h[17]
6. Microbiology – If there is a clinically apparent infection such as meningitis or encephalitis early aggressive treatment should be instituted. Prescribe antimicrobials and antivirals as per trust policy and if required discuss with the microbiology team
7. Blood investigations – see box below

Other general investigations to consider in patients with status epilepticus on admission to critical care

1. Blood investigations
   - Full blood count and clotting screen
   - Urea and electrolytes, liver function tests, calcium, magnesium, blood glucose
   - C-reactive protein (CRP)
   - Arterial blood gas and lactate
   - Peripheral blood culture
2. Urine
   - Toxicology screen – if a toxic cause is suspected (typically tricyclic antidepressants, amphetamines, cocaine, tramadol and some NSAIDS (e.g. mefenamic acid) – urine should be sent for analysis
   - Pregnancy test – in all patients of childbearing age
3. Imaging
   - Chest X-ray for evidence of aspiration
   - CT head if no immediately apparent cause for seizures (e.g. non-adherence with medication)
   - MRI head – as directed by an appropriately experienced clinician
4. Perform lumbar puncture if not contra-indicated by clinical examination and CT head scan findings. CT scan needs to be reviewed by an experienced clinician prior to performing procedure. Send CSF for the following:
   - Microbiology (universal container)
   - Cell count (universal container)
   - Culture and sensitivity including acid fast bacilli (AFB), tuberculosis (TB) PCR and viral PCR for Herpes simplex virus (HSV) 1 and 2, varicella zoster virus (VZV) and Enterovirus sp. Consider wider infection panel in patients who are immunocompromised (universal container)
   - If available, send a Biofire® panel to allow for rapid identification of a range of bacterial, viral or yeast infections
   - Biochemistry
   - Protein (universal container)
   - Glucose (sodium fluoride and potassium oxalate container 'glucose blood tube'); paired serum sample for blood glucose should be sent as well
   - Store CSF sample for future analysis (according to local protocol)

Other general investigations to consider in patients with status epilepticus on admission to critical care

5. Other considerations
   - ECG – if not already performed (daily ECGs are recommended to monitor for features of propofol related infusion syndrome (PRIS) when this agent is being used
   - Admission EEG if the patient remains unconscious without visible seizures
   - Creatine Kinase (CK) ± triglycerides if using high dose propofol (>4 mg/kg/h) or suspicion of rhabdomyolysis (particularly in younger patients)
   - Ideally give phenytoin intravenously and ensure the level is therapeutic. Phenytoin given enterally has erratic absorption and requires the feed to be stopped for a number of hours. See appendix 3 for monitoring and levels.

Additional investigations to be considered for patients admitted with status epilepticus in the absence of seizure history

The list of conditions that have been identified as possible causes of status epilepticus is extensive. No list can be completely exhaustive, however, a recent review provides a comprehensive account.[18] Liaise with a higher level of neurocritical care service for guidance.

Additional investigations include the following:

1. Ammonia levels, urinary organic acids and blood amino acids
2. Vasculitic screen
   - Anti-Nuclear Antibody (ANA), Extractable Nuclear Antigen (ENA), Anti-Neutrophil Cytoplasmic Antibody (ANCA)
   - Complement
   - Serum Angiotensin Converting Enzyme (ACE)
3. Autoimmune Encephalitis Screen (if no other evident aetiology)
   - N-Methyl-D-aspartate receptor (NMDAR) antibodies
   - LGI1 and CASPR2 antibodies (part of voltage gated potassium channel complex)
   - Gamma-aminobutyric acid B receptor (GABABR) antibodies
   - α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) antibodies
   - Gamma-aminobutyric acid A receptor (GABAAR) antibodies
   - Glutamic acid decarboxylase (GAD) antibodies
   - Anti-neuronal (paraneoplastic) antibodies – Hu (ANNA1), Yo (PCA1), Ri (ANNA2), Ma2, CV2 (CRMP5), amphiphysin, SOX1, Titin, Zic4 and DNER (Tr)
   - Thyroid Peroxidase (TPO) antibodies
4. CT Thorax, abdomen and pelvis (CT TAP) with contrast to look for evidence of occult neoplasia, and indirect evidence of paraneoplastic limbic encephalitis.
5. Anticonvulsant drug levels if on anticonvulsants to assess the adequacy of and concordance with therapy.
   - Tests which are not available locally can be sent to the National Drug Monitoring Laboratory, Chalfont Epilepsy Centre. Liaise with the biochemistry or pathology helpdesk of your hospital.

Please also see Appendix 2 *for a summary list of conditions and relevant investigations.*

Continuous electroencephalography (cEEG) monitoring

- Where available, cEEG is advised for patients with an ongoing depressed conscious level or for patients in refractory or super refractory SE. The authors recognise that the availability of cEEG monitoring is very limited and that transferring ventilated patients to a tertiary centre poses significant logistical challenges, requiring substantial manpower, time, and resources; however close collaboration with a tertiary neurocritical care centre is strongly recommended.
- The person reading the EEG should have specialised training in cEEG interpretation, including the ability to analyse raw EEG data as well as quantitative EEG tracings.
- Reduced montage (8-channel EEG) is an acceptable modality for continuous monitoring provided that a sufficient area of the brain can be monitored. Bispectral index (BIS) monitoring is not a suitable alternative to EEG, as it will miss focal seizure activity.

In patients being treated with continuous infusion AEDs, in which most or all convulsive activity resolves, cEEG is the only way to know if treatment is successful.[8]

- cEEG is used to determine whether there is cerebral seizure activity or evidence of subclinical SE. Ideally, cEEG monitoring should be continued for at least 24 h after resolution of seizure activity, while sedated. If it is not feasible to maintain cEEG throughout sedation, then it should be maintained until seizure control is achieved to rule out ongoing subclinical SE.
- Treatment goals include seizure suppression, resting the brain to reduce focal EEG abnormalities and burst suppression.[19–21]
- Management should be overseen by both the critical care consultant and consultant neurologist, due to the potential risk of harm from prolonged sedation and ventilation.

- A cEEG may not currently be available in all critical care units; however, we recommend that all clinical neuroscience centres urgently assess how they could provide this standard of care.
- Where cEEG is not available, extended duration intermittent EEG could be performed to look for resolution of seizures

Continuing or recurrent status epilepticus despite appropriate general anaesthetic therapy for over 24 h (super-refractory SE)

The general anaesthetic agent should be tapered after a minimum of 24 h and if seizures recur either clinically or as evidenced on the EEG, the agent should be recommenced.

There is limited evidence to support any single intervention to control super-refractory seizures so therapy must be directed at treating the underlying cause where possible. Treatment should involve collaborative decision making between consultants in critical care medicine and neurology. Ideally, these patients should be managed in a tertiary neurocritical care centre. A treatment delay reduces the efficacy of the drugs used. Continue treatment as long as there is no evidence of devastating brain injury on MRI (NB significance of high cortical signal on MRI is uncertain as this can be a reversible effect of seizure activity). A favourable recovery can happen weeks to months after super-refractory SE.

The interventions below may be considered[22–26]:

1. Repeat the continuous infusion of general anaesthesia for 48 h using an alternative agent such as thiopentone to suppress pathological changes in the EEG recording.
2. Consider other anaesthetic agents such as intravenous ketamine infusion or volatile inhalational anaesthesia using an agent such as isoflurane.
3. Consider additional anti-seizure medication, for example, lacosamide or phenobarbitone.
4. Ensure magnesium level is within normal range, some units have given additional infusions and aimed for serum level of 1.0–1.5 mmol/L.
5. Consider autoimmune encephalitis, immune-mediated refractory SE, New-Onset Refractory Status Epilepticus (NORSE) or Febrile Infection Related Epilepsy Syndrome (FIRES). **Further management should be directed by a neurologist** and may include immunomodulatory therapy, even in patients with negative serology. First line interventions which been used include pulsed methylprednisolone 1 g/day for 3 days, intravenous immunoglobulin (IVIG) or plasma exchange.[27]

Second line therapies which may be recommended include:

- Rituximab (CD20 monoclonal antibody; 375 mg/m^2 weekly IV infusion for 4 weeks or in adults can also be used as 1 g infusion for two doses, on days 1 and 14)
- Cyclophosphamide (500–1000 mg/m^2 monthly for 3–6 months)
- Tocilizumab (monoclonal antibody against Interleukin-6 receptor; 8 mg/kg monthly for two or more cycles)
- Anakinra (Interleukin-1 Receptor antagonist; up to 5 mg/kg BD)
- Cannabidiol
- Bortezomib (Proteosome inhibitor, especially in NMDAR encephalitis)

Continuing status epilepticus despite the above therapies

1. Re-image the brain for an underlying brain injury.
2. If SE is due to a focal target lesion then consider neurosurgical referral.
3. Interventions occasionally used in tertiary centres.
   - Ketogenic (high fat, low carbohydrate, controlled protein) diet.[28] Liaise with a dietician and pharmacist who are knowledgeable in this area. Ketogenic diets should be used with caution in patients on a propofol infusion since fatty acid oxidation is impaired, potentially leading to an increased risk of propofol infusion syndrome.[29]
   - Single-photon emission computed tomography (SPECT) scanning to evaluate areas of reduced blood flow in the brain.
   - Vagal nerve stimulation in conjunction with specialists in neurology and neurosurgery.[30]

Common causes of treatment failure

1. Continuing NCSE, often due to under-monitoring of EEG or inadequate pharmacological suppression.
2. Failure to establish appropriate maintenance anticonvulsant therapy before the withdrawal of continuous anaesthetic infusion. Hence, ensure maintenance therapy is commenced early in the illness. Particular care should be taken to avoid subtherapeutic phenytoin levels which often occurs in the first few days after the loading dose – see Appendix 3.
3. Rapid weaning of continuous anaesthetic infusion causing rebound seizures after achieving control of SE. If this is the case, a more gradual taper should be attempted.

Dosing of anticonvulsant medications

There are no prospective head to head studies comparing different doses of benzodiazepines and the suggested doses in this document can lead to prolonged periods of somnolence and respiratory depression. Giving lorazepam in titrated aliquots to high risk patients can minimise the risk of these side effects occurring. If the patient

is actively, visibly seizing despite maximum dose benzodiazepine commence anticonvulsants as per doses detailed in Appendix 1.

Where possible the recommended dosing has been taken from the ESETT study.[13] Levetiracetam, fosphenytoin and valproate have been shown to be equivalent. The dosing is for SE only and dosing information continues to evolve. Patients with liver and severe renal impairment were excluded and the trial contained only a small number of patients over 65 years old.

Discussions around which weight to use are ongoing as increasing numbers of patients present at the extremes of the body weight scale. Many of the drugs used have significant drug interactions, including other anticonvulsants and key antibiotics and antifungals. Please consult your pharmacist for assistance with this.

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Abbreviations

ADR	adverse drug reaction
IV	intravenous
IM	intramuscular
IO	intraosseus
NG	nasogastric
ml	millilitres
mmol	millimole
L	litre
kg	kilogram
g	gram
mg	milligram
mcg	microgram
min	minute
h	hour
kPa	kilopascal
cmH_2O	centimetres of water
ECG	electrocardiogram
EEG	electroencephalogram
cEEG	Continuous EEG
CT scan	computed tomography scan
MRI scan	magnetic resonance imaging scan
T	tesla
CSF	cerebrospinal fluid
PE	Phenytoin Equivalents
PEEP	positive end expiratory pressure
PRES	Posterior Reversible Encephalopathy Syndrome
PRIS	Propofol-related Infusion Syndrome
RCVS	Reversible Cerebral Vasoconstriction Syndrome

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Appendix 1 – Detailed Notes on the Acute Management of Seizures in a Hospital Setting

STAGE 1
0 minutes

STAGE 1 - IMMEDIATE MANAGEMENT

- Open and maintain airway
- Consider oropharyngeal or nasopharyngeal airway (if able to insert safely)
- Administer 15L/min oxygen via non-rebreathe mask if to maintain oxygen saturations
- Gain IV/ IO access and take blood arterial blood gas and venous blood for laboratory investigations
- If blood sugar <4mmol/l correct according to local or national guidelines

STAGE 2
0 -15 minutes

STAGE 2 - SPECIFIC MANAGEMENT WITH BENZODIAZEPINE THERAPY

Administer emergency rescue medication

IV Access	No IV Access
Lorazepam 4mg (0.1mg/kg IV/IO (1-2mg aliquots if age >70 or <50kg)	Midazolam 10mg buccal (5mg if patient <50kg)
(Alternatives: Midazolam 10mg / Diazepam 10mg IV/IO	(Alternative: Diazepam 10mg PR)

Wait 5 minutes (Gain IV or IO access if not already done)

If seizures continue then repeat the dose of benzodiazepine after 5-10minutes. Be vigilant for the risk of excessive sedation and respiratory depression with benzodiazepines.

Additional Management

- Continue regular anti-seizure medication if taken prior to admission
- Treat underlying causes (eg hyponatremia or meningitis as per Trust policy)
- Consider iv thiamine (e.g. pabrinex 2pairs tds or IV thiamine 300mg tds) if history of alcohol use or malnutrition

WARD/ EMERGENCY DEPARTMENT

(Continued)

Appendix 1. (Continued)

STAGE 3
15 -30 minutes

STAGE 3 - SPECIFIC MANAGEMENT WITH ADDITIONAL ANTI-SEIZURE THERAPY

URGENT CRITICAL CARE SENIOR DECISION MAKER REVIEW

If seizures not controlled with maximal dose of benzodiazepine therapy

Phenytoin is the only agent licensed for SE. No agent has been shown to be superior to another agent with the choice being patient dependent.

Levetiracetam

60mg/kg IV (maximum dose 4500g) in 100ml of 0.9% sodium chloride or 5% glucose over 10mins. Maintenance dose in normal renal function is usually 1500mg twice a day starting 12 hours after loading dose.

Sodium valproate

40mg/kg IV (maximum dose 3000mg). No standard recommended dilution, for ease use 50-100ml 0.9% sodium chloride over 10mins. Prescribe 20-30mg/kg/day in two- three divided doses 8 hours after loading dose.

Phenytoin

20mg/kg IV (max dose of 2000mg) undiluted or in 100ml of 0.9% sodium chloride over 30-40 mins (max rate 50mg/min).

Infuse at 10- 25 mg/min in elderly and those with possible cardiac disease. Start 100mg TDS IV at least 8 hours after loading dose.

Phenytoin has high pH therefore watch for extravasation if using peripheral line.

If patient continues to seize despite first additional anticonvulsant prepare for and perform rapid sequence intubation and transfer to ICU. Administer a **SECOND** anti-seizure drug from list above.

STAGE 4
30 -60

STAGE 4 - REFRACTORY STATUS EPILEPTICUS MANAGEMENT

CRITICAL CARE

- Please refer patient to neurology team
- Ensure patient is on maximal doses of anti-seizure medications above and all preadmission anti-seizure medication is continued where possible
- Start a continuous infusion of IV propofol (⩽4mg/kg/hr) and/or midazolam (0.1-0.2mg/kg bolus followed by 0.05-0.5mg/kg/hr titrated to effect) after transfer to the ICU. Other agents may be considered if appropriate (appendix 4)
- If possible, commence continuous EEG monitoring
  - Burst suppression pattern may not be initially necessary if there is definite seizure suppression on EEG
  - Discuss EEG findings with consultant neurophysiologist (bedside or via remote viewing)
- If possible, continue EEG monitoring for at least 24 hours following control of seizure activity

STAGE 5
>60 minutes

STAGE 5 - MANAGEMENT OF SUPER-REFRACTORY STATUS EPILEPTICUS (NEEDS AGREEMENT BETWEEN INTENSIVE CARE AND NEUROLOGY TEAM)

Ensure all maintenance anti-seizure medications have been commenced. Additional agents can be added after discussion with the neurology team.

Consider the following to gain control of seizures

1st line	Increase propofol infusion up to maximum of 4mg/kg/hr titrated to effect
2nd line	add midazolam IV 0.1-0.2mg/kg bolus followed by 0.05-0.5mg/kg/hr titrated to effect
3rd line	add lacosamide 200mg IV loading followed by 100mg IV/NG BD 12 hrs after initial loading dose
4th line	add thiopentone 3-5mg/kg bolus followed by 3-5mg/kg/hr titrated to effect

Opioid boluses for seizure control (eg morphine, fentanyl, alfentanil) should be generally avoided, as they are pro-convulsant. Sedation changes should be under guidance of the ICU team. **Ideally use the EEG to guide sedation increases so that they can be titrated to effect.**

Appendix 2 – Differential Diagnoses and Investigations

Many of the following are rare causes of Status Epilepticus. Specialist investigations should be arranged following discussion with the Neurology team.

Category	Condition (investigation)
Vascular	Stroke or intracranial haemorrhage (imaging)
	Vasculitis (imaging, CSF, inflammatory markers, vasculitis screen)
	Vasculopathy - Posterior Reversible Encephalopathy Syndrome (PRES)/
	Reversible Cerebral Vasoconstriction Syndrome (RCVS)/eclampsia (imaging)
Infective	Meningitis (CSF)
	Encephalitis (imaging, CSF)
	HIV (serology, CSF)
	Prion disease (imaging, CSF – discuss with National CJD Research and Surveillance Unit, Edinburgh, EEG)
Neoplastic	Primary or secondary intracranial neoplasm (imaging)
	Malignant meningitis (CSF)
	Lymphoma (imaging, CSF)
	Paraneoplastic limbic encephalitis (imaging, serology, CSF, CT TAP)
Traumatic Brain Injury	Imaging
Autoimmune	Autoimmune encephalitis (imaging, serology, CSF)
	Paraneoplastic limbic encephalitis (imaging, serology, CSF, CT TAP)
	Lupus (serology)
	Neurosarcoidosis (imaging, CSF, serum angiotensin converting enzyme (ACE), chest x-ray or CT TAP)
Metabolic	Derangements of glucose, sodium, calcium, magnesium (blood test)
	Inherited Metabolic Disease (imaging, blood ammonia and lactate, blood amino acids, urinary organic acids, CSF lactate)
	Mitochondrial disease (imaging, blood ammonia and lactate, CSF lactate)
Iatrogenic	Consult your critical care pharmacist, critical illness database, toxbase and summary of product characteristics
Congenital	Congenital structural lesion (imaging)
Pregnancy	Eclampsia

Appendix 3 – Anti-seizure Medication Doses in Status Epilepticus[31-34]

Drug	Loading Dose	Maintenance Dose	Maximum Dose	Mechanism of action	Notes
Midazolam	10mg IV/IO/ Buccal.	N/A.	10mg.	GABA agonist.	If patient weight <50kg, start with 5mg and titrate accordingly. Can be given by buccal route.
Diazepam	10mg IV/IO/ PR.	N/A.	10mg.	GABA agonist.	Halve dose if weight <50kg. Can be given PR.
Lorazepam	0.1mg/kg IV/ IO up to 4mg.	N/A.	0.1mg/kg.	GABA agonist.	Administer in 1-2mg aliquots if weight <50kg or age>70 years.
Levetiracetam	60mg/kg IV.	Dose depends on renal function. If creatinine clearance > 80 mls/ min use1500mg BD.	Max loading: 4.5g. Maintenance: 3g/day.	Synaptic vesicle protein SV2A ligand.	Plasma monitoring is not routinely performed. Needs dose adjustment in renal dysfunction. 1:1 dose conversion when changing from iv to enteral. Caution in patients with suicidal ideation or behaviour. It can cause depression and psychotic symptoms including irritability and aggressiveness.
Sodium Valproate	40mg/kg IV.	20-30mg/kg daily in 2-3 divided doses 8hrs after loading dose.	Loading: 3000mg. Maintenance 2500mg/day.	Sodium channel blocker, calcium channel blocker, GABA modulator.	Recently updated MHRA guidance. Should not be started in female or male patients under the age of 55 unless there is no other effective or tolerated treatment. Risk of teratogenicity in females and infertility in males. Avoid in liver disease, mitochondrial disease and porphyria. Can cause hyperammonemia, pancreatitis, thrombocytopenia. Monitor liver function tests during use. 1:1 dose conversion when changing from iv to enteral.
Lacosamide	200mg IV	100-200mg BD IV	400mg/day. (Max 250mg/ day in end stage renal disease with additional 50% of daily dose to be after hemodialysis).	Enhances slow inactivation of voltage gated sodium channels.	Caution in patients with history of cardiac conduction problems, can cause PR prolongation. Caution in suicidal behavior. 1:1 dose conversion when changing from IV to enteral.
Phenytoin/ fosphenytoin	15-20 mg/kg IV. Infused at max 50mg/ min to avoid bradycardia, prolonged QT and arrhythmias.	Initially 100mg TDS IV (3-5mg/kg)at least8 hours after loading dose	Loading 2000mg.	Sodium channel blocker.	Can cause cardiac arrhythmias and haemodynamic instability. Multiple drug interactions. Monitor liver function tests.

(Continued)

Appendix 3. (Continued)

Drug	Loading Dose	Maintenance Dose	Maximum Dose	Mechanism of action	Notes
Phenytoin/ fosphenytoin	Fosphenytoin is a prodrug which is metabolised to phenytoin within 15 minutes of IV administration. Dosing of Fosphenytoin is expressed as Phenytoin Equivalents (PE). 1.5mg Fosphenytoin = 1mg Phenytoin; 1mg Fosphenytoin PE = 1mg Phenytoin **Conversion from IV to enteral** This should only be done once stable as the absorption of phenytoin is erratic. 1:1 dose conversion when changing from IV to oral capsules / tablets. However, phenytoin suspension is formulated as phenytoin base while capsules and injection are formulated as phenytoin sodium. Therefore, dosage adjustment is required due to the difference in bioavailability when converting from IV / capsules to suspension: 100mg phenytoin sodium (capsules/injection) = 90mg phenytoin base (suspension). **Monitoring Phenytoin** Phenytoin has narrow therapeutic window, high protein binding, non-linear pharmacokinetics and inter-individual variations in metabolism. In the critical care setting there are additional factors including critical illness and drug interactions which affect the distribution and elimination of the drug. Small dose increases can cause large increases in steady state plasma concentrations so plasma monitoring must be performed. Measure levels 2-4 hours after IV loading dose and then measure trough levels every 24 hours after the maintenance dose until levels are stabilized. If levels are below therapeutic range (10-20mg/L) and still fitting, consider top up or loading dose of 5-10mg/kg. **Equations for Corrected Phenytoin Level measurements** Phenytoin is highly protein bound (90%). Serum levels give a total phenytoin level that needs to be corrected to reflect the amount of free phenytoin. **Corrected phenytoin should be calculated where serum albumin is <32g/L: Please consult your pharmacist for input with correct dosing.**				

Appendix 4: Intravenous Anaesthetic Therapy in Status Epilepticus[35,36]

Unless stated and to ensure rapid treatment use patient estimate/actual body weight upto 80kg then use ideal/adjusted body weight.

Drug	Induction Dose	Continuous Infusion			Considerations
		Initial Rate	Breakthrough Dose	Maximum Dose	
Propofol	1 – 2.5mg/kg.	1-4mg/kg/hr.	1mg/kg bolus. Repeated if needed. Increase infusion rate by 0.2mg/kg/hr every 2 hours until flat EEG or burst suppression.	4mg/kg/hr.	Commonly causes hypotension as a side effect. Monitor for evidence of Propofol Infusion Syndrome (PRIS) especially when using high doses for prolonged periods PRIS consists of metabolic acidosis, rhabdomyolysis, renal and cardiac failure with refractory bradycardia. Check plasma triglycerides at least every 2-3 days on high dose propofol. If doses over >4mg/ kg/hr check creatine kinase levels and perform a 12 lead ECG.
Midazolam	0.1 – 0.2mg/kg.	0.05 - 0.5mg/kg/hr.	0.1-0.2mg/kg bolus. Repeated if needed. Increase infusion rate by 0.1mg/ kg/hr every 4 hours until flat EEG or burst suppression.	20mg/hr.	Commonly causes hypotension as a side effect. Tachyphylaxis in long term sedation necessitates increasing doses. May displace phenytoin from albumin–caution when interpreting phenytoin levels. Liver metabolises drug to renally cleared active metabolite so will accumulate in liver and renal failure.
Thiopentone	3-5mg/kg.	3-5mg/kg/hr.	1-2mg/kg. Repeated if needed. Increase infusion rate by 0.5mg/kg/ hr every 6 hours.	8mg/kg/hr.	ADR- hypotension, rhabdomyolysis, hypokalamia. Care with replacement of potassium as it has been pushed unto cells and therefore at risk of rebound hyperkalaemia when discontinued. High frequency potassium sampling should be undertaken to monitor and treat high levels. Zero order pharmacokinetics, Has a large volume of distribution, so needs repetitive boluses and accumulates in adipose tissue which can lead to a a long washout time. Plasma thiopentone levels are not routinely indicated. Use of thiopentone implies a 5 days wait post-infusion for brainstem testing.
Ketamine	0.5 – 2mg/kg.	1 –5 mg/ kg/hr. Initially 2mg/ kg/hr.	1mg/kg bolus. Repeated if needed.	7.5mg/kg/h.	Lack of controlled studies in SE. Limited reports of ADRs- possibly hypertension, psychiatric symptoms. Hypotension and respiratory depression are rarely encountered.

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